(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 20,000 units of penicillin G per milliliter.

(4) [Reserved]

(5) *Loss on drying.* Proceed as directed in § 436.200(b) of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 60 milligrams per milliliter.

(7) *Penicillin G content.* Proceed as directed in § 436.316 of this chapter.

(8) *Crystallinity.* Proceed as directed in § 436.203(a) of this chapter.

(9) *Heat stability.* Proceed as directed in § 436.214 of this chapter.

[42 FR 59861, Nov. 22, 1977, as amended at 45 FR 22922, Apr. 4, 1980; 50 FR 19918, 19919, May 13, 1985]

§ 440.83a Sterile piperacillin sodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile piperacillin sodium is the sodium salt of (2*S*,5*R*, 6*R*)-6-[(*R*)-2-(4-ethyl-2,3-dioxo-1-piperazine-carboxamido)-2-phenylacetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate. It is so purified and dried that:

(i) Its potency is not less than 863 micrograms and not more than 1,007 micrograms of piperacillin per milligram on an anhydrous basis. If it is packaged for dispensing, it contains not less than 90.0 percent and not more than 120.0 percent of the number of grams of piperacillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 1.0 percent.

(vi) Its pH in an aqueous solution containing 400 milligrams per milliliter is not less than 5.5 and not more than 7.5.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, and pH.

(ii) Samples required:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.334 of this chapter.

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(a) of this chapter, using a solution containing 150 milligrams of piperacillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter, using the sample preparation method described in paragraph (d)(4) of that section.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 400 milligrams per milliliter

[47 FR 15769, Apr. 13, 1982, as amended at 50 FR 19918, 19919, May 13, 1985]

§ 440.90a Sterile ticarcillin disodium.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Sterile ticarcillin disodium is 6-[(carboxy-3-thienylacetyl)] amino - 3, 3-dimethyl - 7 - oxo - 4 - thia - 1 - azabicyclo[3.2.0]heptane-2-carboxylic acid disodium salt. It is so purified and dried that:

(i) It contains not less than 800 micrograms of ticarcillin per milligram on an anhydrous basis. If it is packaged for dispensing, its ticarcillin content is not less than 90 percent and

not more than 115 percent of the number of milligrams of ticarcillin that it is represented to contain.

(ii) It is sterile.

(iii) It is nonpyrogenic.

(iv) [Reserved]

(v) Its moisture content is not more than 6.0 percent.

(vi) Its pH in an aqueous solution containing 10 milligrams of ticarcillin per milliliter (or if packaged for dispensing after reconstitution as directed in the labeling) is not less than 6.0 and not more than 8.0.

(vii) It gives a positive identity test for ticarcillin.

(viii) Its ticarcillin content is not less than 80 percent and not more than 94 percent on an anhydrous basis.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, sterility, pyrogens, moisture, pH, identity, and ticarcillin content.

(ii) Samples required:

(*a*) If it is packaged for repacking or for use in the manufacture of another drug:

(*1*) For all tests except sterility: 10 packages, each containing approximately 300 milligrams; and 5 packages, each containing approximately 1 gram.

(*2*) For sterility testing: 20 packages, each containing approximately 300 milligrams.

(*b*) If it is packaged for dispensing:

(*1*) For all tests except sterility: A minimum of 15 immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 436.105 of this chapter, preparing the sample for assay as follows: Dissolve an accurately weighed sample in sufficient 1.0 percent potassium phosphate buffer, pH 6.0 (solution 1), to give a stock solution of convenient concentration; and also, if it is packaged for dispensing, reconstitute as directed in the labeling. Then using a suitable hypodermic needle and syringe, remove all the withdrawable contents if it is represented as a single-dose container; or if the labeling specifies the amount of potency in a given volume of the resultant preparation, remove an accurately measured representative portion from each container. If it is a single-dose container, use a separate needle and syringe for each container. Dilute with sufficient solution 1 to give a stock solution of convenient concentration. Further dilute an aliquot of the stock solution with solution 1 to the reference concentration of 5.0 micrograms of ticarcillin per milliliter (estimated).

(2) *Sterility.* Proceed as directed in § 436.20 of this chapter, using the method described in paragraph (e)(1) of that section.

(3) *Pyrogens.* Proceed as directed in § 436.32(b) of this chapter, using a solution containing 100 milligrams of ticarcillin per milliliter.

(4) [Reserved]

(5) *Moisture.* Proceed as directed in § 436.201 of this chapter.

(6) *pH.* Proceed as directed in § 436.202 of this chapter, using an aqueous solution containing 10 milligrams of ticarcillin per milliliter (or if packaged for dispensing, use a solution prepared as directed for reconstitution in the labeling).

(7) *Identity and ticarcillin content.* Transfer an accurately weighed portion of approximately 40 milligrams of the sample to a 100-milliliter volumetric flask. Dissolve and dilute to volume with distilled water. Transfer 5.0 milliliters of this solution to another 100-milliliter volumetric flask and dilute to volume with 0.1*N* methanolic hydrochloric acid (prepared by diluting 0.8 milliliter of 12*N* hydrochloric acid to 100 milliliters with methyl alcohol). Treat a portion of the ticarcillin standard in the same manner. Using a suitable spectrophotometer equipped with a 1.0-centimeter quartz cell and 0.1*N* methanolic acid as a blank, scan the absorption spectrum of the methanolic solution of the sample and the standard between the wavelengths of 300 and 200 nanometers. Determine the absorbance of each solution at the maxima, at approximately 230 nanometers. The spectrum of the samples should compare qualitatively with

that of the ticarcillin working standard. Determine the percent ticarcillin as follows:

$$\text{Percent ticarcillin} = \frac{\text{Absorbance of sample} \times \text{Weight in milligrams of standard} \times \text{Potency of standard in micrograms per milligram} \times 10}{\text{Absorbance of standard} \times \text{weight in milligrams of sample} \times (100 - m)}$$

where: m=Percent moisture in the sample.

[42 FR 14093, Mar. 15, 1977, as amended at 50 FR 19918, 19919, May 13, 1985]

§ 440.91 Ticarcillin monosodium monohydrate.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Ticarcillin monosodium monohydrate is 6-[(carboxy-3-thienylacetyl)] amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid monosodium salt monohydrate. It is so purified and dried that:

(i) Its ticarcillin potency is not less than 890 micrograms of ticarcillin per milligram calculated on an anhydrous basis.

(ii) Its moisture content is not less than 4.0 and not more than 6.0 percent.

(iii) The pH of an aqueous solution containing 10 milligrams of ticarcillin per milliliter is not less than 2.5 and not more than 4.0.

(iv) It gives a positive identity test for ticarcillin.

(v) It is crystalline.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 432.5 of this chapter.

(3) *Requests for certification; samples.* In addition to complying with the requirements of § 431.1 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, moisture, pH, identity, and crystallinity.

(ii) Samples, if required by the Center for Drug Evaluation and Research: 10 packages, each containing approximately 300 milligrams.

(b) *Tests and methods of assay*—(1) *Ticarcillin potency.* Determine the micrograms of ticarcillin activity per milligram of sample. Proceed as directed in § 436.355 of this chapter using the equipment, conditions, reagents, and system suitability requirements as described in § 440.290b(b), except use the resolution test solution to determine resolution in lieu of the working standard solution. Prepare the working standard solution, sample solution, and resolution test solution and calculate the micrograms of ticarcillin per milligrams as follows:

(i) *Preparation of working standard, sample, and resolution test solutions*—(A) *Working standard solution.* Accurately weigh a quantity of the ticarcillin working standard containing the equivalent of approximately 90 milligrams of ticarcillin activity and transfer to a 100-milliliter volumetric flask. Dissolve and dilute to volume with diluent pH 6.4 phosphate buffer prepared as described in § 440.290b(b)(1)(i)(*c*).

(B) *Sample solution.* Dissolve an accurately weighed portion of the sample with diluent pH 6.4 buffer as prepared in § 440.290b(b)(1)(i)(*c*) to obtain a solution containing 0.9 milligram of ticarcillin activity per milliliter (estimated).

(C) *Resolution test solution.* Accurately weigh a quantity of the ticarcillin working standard containing the equivalent of approximately 90 milligrams of ticarcillin activity and transfer to a 100-milliliter volumetric flask. Prepare a solution of the clavulanic acid working standard containing the equivalent of 30 milligrams of clavulanic acid activity in a 100-milliliter volumetric flask. Dissolve and dilute to volume with diluent. Transfer 10 milliliters of this solution into the flask containing the ticarcillin standard. Dilute the combined standard solution to volume with diluent and mix. Use within 8 hours of preparation.